SECTION 7

CALCIUM AND VITAMIN D INTERVENTION

INTRODUCTION

The objective of the Calcium and Vitamin D (CaD) component of the Clinical Trial (CT) is to determine the effect of supplementation with calcium and vitamin D primarily on the incidence of hip fractures and secondarily on the incidence of colorectal cancer, other types of fractures, other cancers, cardiovascular disease, and mortality. The addition of vitamin D to calcium supplementation is thought to enhance the effect of the calcium on the prevention of bone loss.

One year after randomization into the CT—Hormone Replacement Therapy (HRT) and/or Dietary Modification (DM)—eligible participants will be invited to join the CaD component. Participants have the option of taking one of two forms of CaD: chewable or swallowable. If they are interested in and eligible for CaD, participants will be randomized in a double-blind fashion into one of two arms:

- CaD intervention:

  1. **Chewable**:

     Chewable calcium carbonate 1000 mg elemental calcium per day, plus vitamin D3 400 IU per day (dispensed as two chewable tablets, each containing 500 mg of elemental calcium and 200 IU of vitamin D).

  2. **Swallowable**:

     Calcium carbonate 1000 mg elemental calcium per day, plus vitamin D_3 400 IU per day (dispensed as two **swallowable** pills, each containing 500 mg of elemental calcium and 200 IU of vitamin D). *Note:* dosage of Vitamin D changed from 125 IU to 200 IU in Spring 1998

- CaD placebo:

  A placebo calcium and vitamin D tablet that appears identical to the intervention tablet (dispensed as two chewable tablets or two swallowable pills of placebo)

It is estimated that approximately 45,000 women will be randomized to the CaD component (1,125 at each Clinical Center [CC]). Guidelines and requirements for implementation of the CaD component of the CT are included in this section. Each CC may devise policies and schedules for themselves within these recommendations and requirements to produce optimal performance in the Women's Health Initiative (WHI) CaD component and to provide appropriate care and follow-up of participants.

7.1 Recruitment and Randomization (Required)

Historically, if a participant was interested and eligible for the CaD component, she was invited to join the CaD component before her first annual visit (AV1) *or* she could be invited to join her second annual visit (AV2) if she had not been offered CaD at AV1. In March 1998, the Steering Committee approved offering the CaD component through AV2 for all participants (as well as between AV1 and AV2, at the clinic's option). Participants can be invited to join CaD at AV1 up to AV2, and randomized up to 2 months past the AV2 target date. Note that CCs are still required to offer CaD at AV1.

The procedures below describe the process for the AV1 or AV2, and can also be applied to any visit. For CaD randomizations between AV1 and AV2, the visit type must be marked according to the most recent routine contact (AV1 or SA2), not as a non-routine contact.

7.1.1 Preparation for the Annual Visit (Recommended)

Run a CaD eligibility determination on the participant from the WHILMA database before the target annual visit date. This eligibility determination will indicate if the participant is eligible for CaD based on medical history information received to date.

If the CaD eligibility determination returns a result other than "INEL" [WHILMA will not give an "eligible" result at this time], include in the pre-visit packet of materials (e.g., appointment reminder, *Form 33 - Medical History Update,* and *Personal Information Update - WHIP 0441*), the *Invitation to Join CaD* (see *Appendix F*) and your CC's CaD consent form. Mail this packet out to the participant at least two weeks before the appropriate annual visit. This CaD information should also be presented and reviewed with the participant at the annual visit.

The day before the annual visit, place two copies of your CC's CaD consent form, *Form 11 - Consent Status,* and *Form 16 - CaD Eligibility Assessment* in each eligible CT participant's annual visit file along with barcode labels with the participant's ID and name. The labels should NOT be applied to forms until the participant arrives for the visit. Additionally, labels should not be applied to medication bottles until randomization, when the WHILMA medication selection function is enacted.

7.1.2 Activities During the Annual Visit (Required)

CaD-related activities during the appropriate annual visit include:

- Determining the participant's interest in and eligibility for CaD.
- Providing her with complete information about the CaD component.
- Offering her a taste test of the chewable tablet, and/or a swallow test of the swallowable pill.
- Obtaining informed consent.
- Randomizing her to a CaD treatment arm.
- Selecting and dispensing a 6-month supply of CaD study pills.

Refer to *Volume 2, Section 16.3 - Annual (CT) and Third-Year (OS) Visit* for additional annual visit activities.

7.1.3 Eligibility (Required)

Participants who have been randomized and followed for at least one year in one or both of the other CT components (HRT and/or DM) are eligible for CaD. Participants enrolled in the Observational Study (OS) are **not** eligible for CaD. Participants interested in the CaD component must meet specific eligibility criteria before they can be randomized.

Eligibility criteria (and data sources) that must be met for CaD randomization include:

- Currently randomized to HRT and/or DM (WHILMA database).
- Willing to participate in CaD (*Forms 11* and *16*).
- Survivability of **>** 3 years (Clinical Practitioner (CP) judgment on *Form 16*).
- No history of hypercalcemia (*Form 16*).
- No history of renal calculi *(Form 16*).
- No kidney failure requiring dialysis (CP judgment on *Form 16*).
- No current daily oral use of corticosteroids (*Form 16*).
- No current use of calcitriol (*Form 16*).
- No dementia (CP judgment on *Form 16*).
- Vitamin D intake of less than or equal to 600 IU daily or willingness to decrease daily use to 600 IU or less (*Form 16*).
- Randomization up to two months past the AV2 target visit date.

Before *Form 16* is entered, the WHILMA eligibility determination for CaD is based on:

- *Form 30 – Medical History* (from screening).
- *Form 33 - Medical History Update* (from semi-annual visit).

If these data indicate no previous hypercalcemia or renal calculi (WHILMA result is not "INEL"), the participant is currently eligible for CaD and can be invited to the CC to further assess interest and eligibility.

7.1.4 CaD Information and Consent (Required)

The following procedures are required before the participant can be randomized.

7.1.4.1 CaD Study Pill Taste/Swallow Test Procedure

Overview

Clinical Centers are required to:

- Explain the option to take a chewable tablet or swallowable pill.
- Provide participants with a visual inspection of the CaD study pills.
- Offer a taste test and/or swallow test before CaD randomization.

It is recommended that these procedures be implemented during the informed consent discussion. Note that the participant can decline either test.

McKesson will supply separate bottles of CaD study pills for the taste and swallow tests, marked "CaD Taste Test" or "CaD Swallow Test." Neither the CC staff nor the participant will know if the tablet or pill being tested is the active or placebo study pill. Reorder additional "CaD Test" bottles from McKesson as needed.

Visual Inspection

When introducing the visual inspection of both formulations, emphasize the importance of the WHI CaD study for learning about whether the calcium and vitamin D can prevent broken bones and colon and rectal cancer. Stress the need for such scientific studies before prevention strategies can be recommended generally with

confidence. Tell the participant that you are going to show her a study pill similar to the one she would take as a participant in this part of the WHI. Drop a study pill from each bottle into their bottle caps for the participant to view (do not touch the study pills with your hands). Tell her the study pills are:

Chewable Tablet

- Meant to be chewed (but can also be crushed and swallowed with water or soft food).
- Peppermint-flavored.
- Similar to other chewable calcium tablets (like Tums®).

Swallowable Pill

- Meant to be swallowed with water.
- Similar to other swallowable pills .

Taste/Swallow Test

Tell the participant that the taste or consistency of the chewable tablet might seem a little different and encourage her to try one. If she refuses either or both tests, let her know this is optional but recommended. Recommend that she also try the swallowable pill. If she declines, throw the study pills used for visual inspection away in their respective study pill discard boxes.

If she agrees to the taste and/or swallow test, drop the appropriate pill from the bottle cap into her hand (again, not touching the tablet). As she tastes the chewable tablet, ask her to pay attention to its:

- taste
- consistency
- chewability

Give her a glass of water. As she tries the swallowable pill, ask her to pay attention to its:

- taste
- ease of swallowing

Evaluation and Follow-Up

Ask the participant if she has any questions about the study pills or the CaD study. Remind her that once she joins, no one can take her place. Refer to the *Questions and Answers: Calcium and Vitamin D Trial (for CC staff) (Appendix G - CC Reference Materials)* for answers to her questions.

Assess the participant's response to the visual inspection and the test of either or both formulations. CCs are encouraged to develop local strategies and guidelines for evaluation. Document on *Form 16 – CaD Eligibility Assessment* her formulation preference (chewable or swallowable). If the participant declines to participate in CaD, complete the staff impression item on *Form 16 - CaD Eligibility Assessment*. Be sure to let her know that her continued participation in the other clinical trial component(s) (i.e., HRT and/or DM) is important, very much appreciated, and will not be affected by declining participation in CaD. If the participant requests more time to decide, you may recontact her up to 2 months past the AV2 target visit date.

Document the participant's response to the visual inspection and the taste and/or swallow tests in the participant's contact notes. This information will help other staff who have future contact with the participant.

7.1.4.2 Informed Consent (Required)

Provide the participant with adequate information and time to give informed consent to CaD if she:

- Is currently eligible for the CaD component, according to the pre-visit eligibility determination.
- Has read the CaD consent mailed to her before or provided during the visit.
- Is interested in participating in CaD.

Begin an information-sharing session about the CaD component in a quiet, private area away from possible interruptions. During this session, review the CaD consent form with the participant and answer any questions she may have. A suggested script you might follow is contained in *Figure 7.1 – CaD Consent Script*. If you do not follow this script, however, you **must** cover the following points:

- The CaD study is completely voluntary and the participants may withdraw at any time. If she does chose to withdraw, no one else can take her place. Her decision will not affect her involvement in the other WHI component(s) to which she is randomized.

- Any information she gives will be held completely confidential and will be released to no one except WHI personnel and, if necessary, authorized Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) staff.

- Her response will be added to those of other women and only composite or grouped information will be released. Neither her name nor any other identifying information will be released in WHI reports or publications.

- The assignment to treatment groups is completely random, a computer makes the selection and both groups are equally important.

- **Study Pills:** The participant will be asked to take one CaD chewable tablet or swallowable pill two times a day (with meals). The pills will contain either active calcium and vitamin D or no supplements (placebo). The CaD study pills may be dispensed on an annual basis (if she has tolerated at least 6 months of the same formulation) or every 6 months. The participant may switch formulations at any time. After randomization is complete, the participant must limit her personal use of vitamin D to less than or equal to 1,000 IU.

- **Schedule:** The participant will be monitored at the same schedule as her other WHI component(s), with the exception that she will be interviewed every six months to discuss any symptoms or health events to be sure that taking pills is still safe for her.

- **Risks:** Some participants may notice short-term gastrointestinal side effects (constipation, bloating, or gas). There is a very small risk of more serious problems such as high blood calcium or kidney or bladder stones.

The CaD consent form must be signed and dated after the appropriate CC staff person reviews the content in detail with the participant, she had had the chance to ask questions, and she agrees to participate. The appropriate WHI signer should be determined by your PI and approved by your local Institutional Review Board (IRB) (some IRBs may require a specific signer and/or witness). You must give the participant one copy of the consent form to take home with her and place a signed copy of the consent form in her file.

Some participants may want to go home and discuss this decision with others before agreeing to participate. Provide these participants with a stamped, addressed mailing envelope and two copies of the consent form (so they can mail in a signed copy and keep the other) or plan to copy the signed consent form after it's returned and mail it back to the participant. Your local Institutional Review Board (IRB) may have specific guidelines for consent by mail. Note that the participant should **not** be randomized to CaD and CaD study pills should **not** be dispensed until the signed consent is received.

After a thorough informed consent discussion and adequate opportunity to consult with others, document the participant's decision on *Form 16 - CaD Eligibility Assessment*. If the participant is interested in joining CaD, obtain her signature on the CaD consent form, obtain additional signatures as required by your IRB, provide her with a copy of the consent, and complete *Form 11 - Consent Status*. If she is not willing to participate, record this information on *Form 16 - CaD Eligibility Assessment* and continue to follow her for the other clinical trial components in which she is participating.

7.1.5 Randomization Activities (Required)

The final eligibility determination for and randomization to CaD is a WHILMA database function that requires data entry of *Form 11 - Consent Status* (with contact date of less than 6 months) and *Form 16 - CaD Eligibility Assessment* (with contact date of less than 1 month).

To randomize a participant to CaD, enact the WHILMA randomization function and record appropriate information on *Form 8 - Randomization/Enrollment Log*. Randomization to CaD occurs at a ratio of 50:50, active treatment:placebo.

7.1.6 Implementing the CaD Intervention After Randomization

The CaD intervention consists of the study pills, the *CaD Handbook* (see *Appendix F.3.15*), and discussions with participants on the specifics of the intervention. Use the four steps below and the information sheet when initially providing the study pills to each participant after randomization. Review them, as necessary, at subsequent contacts.

Step 1 - Introducing the CaD Intervention to the Participant (Required)

Providing the CaD Handbook

Welcome the participant to the CaD and congratulate her on her participation so far. Hand her a copy of the *CaD Handbook*. Explain that this handbook contains the basic information she will need and that you and she will cover some of it right now. Tell her that if she ever has any questions she should ask them as you go along so that she will not forget them.

Reviewing the Importance of the CaD

Review the importance of the CaD to women's health and to the field of prevention science. Remind the participant of her importance to the study and of her generosity in volunteering her time and effort. Discuss the scientific outcomes of the study (e.g., effects of CaD on bone fractures and colorectal cancer). Also reassure the participant by emphasizing the safety points in the CaD. Use the *Questions and Answers: Calcium and Vitamin D Trial (for CC staff)* (in *Appendix G*) to help guide your responses.

Step 2 - Taking the CaD Study Pills

CaD study pills are bottled as 215 pills per bottle for the chewable or 430 pills per bottle for the swallowable formulations. Dispense one or two bottles (depending on the formulation) at randomization to cover the first six months, according to the procedures outlined in *Section 15.4.5 - Dispensing CaD Study Pills.* Clinical Centers should dispense only a 6-month supply of either formulation until the participant has been tolerant and adherent of the **same** formulation for at least one year.

Instructions for Taking Pills (Required)

Describe the label contents to the participant. Offer her a non-child resistant cap. (See *Section 15.1.3. - Child-Resistant Caps*.) Review with the participant the *CaD Handbook* (given above), telling her:

- To take one study pill two times each day with meals (e.g., one with breakfast and one with dinner).
- To chew the tablet or swallow the pill (show the participant how to do this). The chewable tablet may be broken into small pieces to swallow with water.
- To contact the CC if she is having any problems taking the study pills. The CC staff can provide options that may make it easier to take the study pills.
- That she may have minor symptoms (e.g., constipation, bloating), what she can do about them, and what symptoms warrant contacting a health care provider (i.e., flank pain or bloody urine).

It is recommended that you caution the participant not to shake the bottle of CaD chewable tablets excessively because the pills easily crumble. If the participant's randomization to CaD occurs after she has left the CC (but within the 2-month window around the target visit date), CaD study pills can be selected, dispensed, and sent to her through the mail. Along with the study pills, mail out the *CaD Handbook* and confirm by telephone that she understands the instructions. If the participant wants a non-child resistant cap, she must sign the appropriate consent form.

Using the Pill Organizer (Recommended)

Give the participant one or two seven-day pill organizers (if needed) and show her how to use it as a reminder to take her pills. Discuss using it also for other medications she may take. Let her know that she can have **two** pill organizers (one for the morning, one for the evening) to help her remember both pills each day (this may be particularly useful if she also takes other medications).

Designing a Reminder System (Recommended)

Ask the participant how she is going to remember to take the pill every day. Ask her about other pills or daily activities she has and how she remembers to do these things. Help her to integrate the CaD study pill with other daily pills or activities. If she (or you) seems concerned with her ability to remember, or she indicates that she has had trouble in the past remembering to take pills or perform other daily activities, help her to design a cueing or reminder system to help her remember. Explain what a cue is (a cue is anything that will remind the participant to take her pill every day—e.g., pill organizers, post-it notes on refrigerators or mirrors). Consider time of day, placement of cue or reminder, ease of seeing the cue, and consistency of the cue, when designing the reminder system. Ask the participant how she will remember to take her study pills when she is in an unusual situation (e.g., on vacation, traveling, or weekends).

Identifying and Building Skills (Recommended)

Ask the participant if she thinks she will be comfortable performing the activities needed to participate in the CaD intervention. Discuss those activities that she expresses concern about. Ask her to rehearse interactions or activities with you about which she is uncertain. Recommend specific behavioral goals and identify steps to achieve the goals. For example, remembering to take pills daily could include cueing the participant for a specific time and place to take the pill, having a supply of pills to take at that time and place, and being assertive in order to take the pill in the presence of others. Ask her to try out the new behaviors and let you know how they work at the next contact.

Review (Recommended)

Review the steps involved in taking CaD study pills with the participant. Ask the participant questions that allow you to be sure she understands all the information and is ready to participate. An example of such questions includes, "How are you going to remember to take your pills?" Remind her to call with any questions.

<u>Step 3 - Understanding Symptoms</u> (Recommended)

Identify Fears and Beliefs

Ask the participant what she is feeling about starting on the pills. Identify any fears, worries, or apprehensions that she may have about taking study pills. Ask her if she, her friends, or family members have had negative experiences with taking calcium or vitamin supplements. Ask her what she expects to happen to her and what the consequences of these events will be. Listen and acknowledge the participant's beliefs about CaD and correct any misperceptions she may have.

Reviewing Possible Symptoms

Discuss with the participant possible symptoms that she may experience. Indicate that each woman is different and that her experience may be the same or different from other women. Discuss her trial experience to date. Emphasize the long-term nature of the program, including long-term gains. Discuss with her the ways that the trial procedures promote participant safety and remind her that if she has any questions or problems she should call the CC right away.

Review

Review the issues she brought up about her previous experiences and beliefs about CaD. Also, identify any issues about which you have more up-to-date information to allay any fears and concerns in the future.

Step 4 - Discussion of Routine Monitoring (Recommended)

Reasons for Monitoring

Explain to the participant the reasons for monitoring (i.e., ensuring the safety of the participant and collecting follow-up data).

Monitoring Activities

Review the basic schedule of follow-up and monitoring that occurs as part of the CaD. Ask the participant questions to determine if she understands her responsibilities and activities in the trial and the reasons for them. Ask her if she has any other questions at this time.

7.1.7 Exit Interviews (Recommended)

Review the visit activities with the participant to be sure you completed all the necessary tasks, built rapport, and fostered a commitment to the study.

Be sure that the newly randomized participant has appropriate CaD materials to take home (in addition to those for the other CT components) including:

- Clinical Center-specific CaD consent form (required).
- *CaD Handbook* (required; see in *Appendix F.3.15*).
- A 6-month supply of CaD study pills.
- One to two WHI pill organizers (if needed; can be ordered annually with quarter 3 orders on *Form 172 - Supplies Order*).
- CaD chart labels (optional; can be ordered quarterly on *Form 172* and given to participant or sent to her primary care provider).
- Confirmation of randomization (optional).

Inform the participant about what to expect at the next 4-week contact and answer any questions she may have. Remind her to contact the CC any time she has questions or concerns.

7.2 Follow-Up Contacts with CaD Participants

After CaD randomization, a phone contact at four weeks (with a target window of ± two weeks on either side) is required (see *Section 16.1 - Early Adherence & Safety Contact*). Otherwise, CaD follow-up, as with the other CT components, occurs every 6 months. Follow-up procedures for CaD participants are essentially the same as those required by the participant's initial trial component (HRT and/or DM) with semi-annual contacts (phone, mail, or visit as appropriate and determined by CC) and annual visits. Note that a CaD participant should only be dispensed a 6-month supply of CaD study pills until she has tolerated the same formulation for an entire year.

Before each semi-annual contact and annual visit, remind all CaD participants to bring in (or mail in, as appropriate) their CaD study pills, including those in their bottles and pill organizers.

7.2.1 Forms Review (Required)

Complete *Form 17 - CaD Management and Safety Interview* and review at each semi-annual and/or annual contact for any new-onset renal calculi, hypercalcemia, vitamin D or calcitriol use that would necessitate permanently discontinuing her CaD study pills (see *Section 7.3 - Adverse Effects*). Note the participant may opt to change study pill formulation at this time.

Review her *Current Supplements (Task 45*), if appropriate, to confirm she is not taking more than 1,000 IU of vitamin D daily. If she is taking > 1,000 IU daily and is unwilling to decrease her dose, discontinue her CaD study pills. They may be restarted if she decreases her dose of vitamin D (to ≤ 1,000 IU) in the future.

Complete *Form 54 - Change of Medications* if you temporarily change or discontinue her CaD study pills or *Form 7 - Participation Status* if she changes intervention status permanently.

7.2.2 Identifying Problems at Participant Contacts

Use every contact with a participant to identify issues or problems with pill-taking, symptoms or safety, adherence, and retention. Review *Section* 17.2.3 - *Reasons for Poor Retention and/or Adherence* to identify potential reasons that participants would stop or decrease pill taking. Use the steps below to identify adherence problems.

Step 1 – Adherence Collection (Required)

At each semi-annual contact and/or annual visit, as appropriate, weigh the participant's returned CaD bottles or have the participant provide an estimated count. Refer to *Section 15.6.2 - Adherence Assessment* for pill weighing and pill estimation procedures and appropriate troubleshooting.

Step 2 - Monitoring Adherence and Symptoms (Recommended)

Adherence is defined as taking CaD study pills at 80% of the appropriate amount or higher. WHILMA will estimate this at follow-up using the participant's bottle weight.

7.2.2.1 Switch of Formulations

At each contact with a participant, evaluate the potential benefit of switching formulations. Refer to *Figure 7.2 – New CaD Formulation Scripts* for suggested scripts to use when a participant is asked to consider switching formulations.

7.2.2.2 Intensive Adherence Plan (Required)

Refer women who have adherence assessed at < 80%, or seem at risk for low adherence, to the appropriate Intensive Adherence Plan (IAP) coordinator. See *Section 17.2.2.2 – Initiating Special Activities for HRT and CaD Retention Challenges [IAP]*).

7.2.3 Dispense Study Pills (Required)

Select and dispense to the participant another 6- to 12-month supply of CaD study pills. Provide the participant with another *CaD Handbook* and pill organizer, if needed. If she has been having trouble with remembering the study pills or taking them twice a day, offer her the option of taking two pills once a day (see *Table 7.1 - Step-Down Procedures for Managing Adherence Problems or Minor Adverse Effects).*

7.2.4 Osteoporosis Handout

CCs are not required to give the *WHI Update – What You Should Know About Osteoporosis* and guidelines to participants. However, if CCs decide to give participants information on osteoporosis, they must use this handout. (See *Appendix F – Required CC Printed Materials, Figure F.3.11*.)

Table 7.1

Step-Down Procedures for Managing Adherence Problems or Minor Adverse Effects*

Participant Problem	**Initial Option to Offer**	**Other Options if Problem Doesn't Resolve (prioritized)**
Taking study pills with food (difficulty remembering or having food available)	Try taking study pills without food and re-evaluate for possible minor adverse effects (see below)	N/A
Remembering to take pills twice a day (even using the WHI pill organizer)	Take two pills once a day for one to three months and re-evaluate.	N/A
Taking the specific study pills (e.g., too big, don't like the taste, can't swallow)	Change to the other formulation and re-evaluate	Crush/break/cut the chewable tablet. Mix the pieces up with liquid or soft foods and/or simply chew or swallow the pieces, as tolerated. Cut the swallowable tablet (provide her with information about pill cutters) and swallow the pieces individually. Take two pills once a day for one to three months and re-evaluate. You may need to step down further to one pill once a day, if necessary to retain the participant).
Experiencing GI symptoms or other minor adverse effects	Take only one pill once a day for one to three months and re-evaluate	Take only one pill every other day (or every two to three days) for one month and re-evaluate. Stop taking pills for one month and re-evaluate

*Note that you should continue to re-evaluate these problems and options (at routine or non-routine contacts) and, if possible, bring the participant back up to the study regimen (one study pill twice a day).

7.3 Adverse Effects

Trial participants may experience adverse effects ranging from mild inconvenience to more serious conditions. Take time to identify potential adverse experiences early so that appropriate and prompt treatment, referral, and study medication stoppage decisions can be made. Participants are informed about possible major and minor effects of calcium and vitamin D before randomization (when informed consent is obtained) and after randomization (each time study pills are dispensed). The *CaD Handbook* also reviews these adverse effects. (See *Vol. 2, Appendix F*.)

7.3.1 Monitoring for Adverse Effects (Required)

Information about CaD adverse effects may be collected from:

- *Form 17 - CaD Management and Safety Interview.*
- *Form 33 - Medical History Update* or *Form 33D - Medical History Update (Detail)*
- Participant calls to the CC between visits.
- Reports of symptoms to CC staff during scheduled or unscheduled contacts.

Adverse effects that are life-threatening and previously unassociated with CaD constitute serious adverse effects (SAEs) and must be reported to the Program Office and the Clinical Coordinating Center (CCC). See *Section 15.7.2.2 - Reporting SAEs.*

7.3.2 Minor Adverse Effects (Required)

Few minor adverse effects are anticipated with the CaD component. Minor adverse effects that have been reported in the past have usually been gastrointestinal (GI) in origin. Not all women will have such symptoms, and the severity and frequency of symptoms will vary among women, as will their responsiveness to symptom management or dosage changes. These symptoms are often noted with any medications or placebo pills. Therefore, remind the participant that these changes may not be due to the study pills. When the participant starts on CaD study pills, inform her of the possible minor adverse effects that could occur as listed on the *CaD Handbook.*

Tell her that these symptoms are in most cases not harmful, but that she should contact the CC if any of the symptoms become severe or very uncomfortable. Reassure her that most minor symptoms associated with CaD study pill use resolve spontaneously and within 2-3 months.

7.3.2.1 Management of Minor Symptoms

Management of minor adverse effects of CaD is primarily palliative or symptom-related. If the participant reports GI symptoms, reassure her that these symptoms may not be due to the study pills and that serious side effects of CaD therapy are rare. Remind her to take her study pills with meals if she is experiencing minor adverse effects. Review the *CaD Handbook* with the participant and recommend that she also try other simple strategies for managing these minor symptoms at home, such as increasing fluid intake. Also refer to *Questions and Answers: Calcium and Vitamin D Trial (for CC staff)* (*Appendix G.1.1*) for guidance with your responses. Encourage her to call the CC if she has any questions or problems.

If symptoms are intolerable or severe enough that participant adherence/retention is a threat, step-down her dose to one study pill per day (or one study pill every other day or every one to two days, as tolerated) with meals for one to three months. See *Table 7.1 – Step-Down Procedures for Managing Adherence Problems or Minor Adverse Effects.* After this time period, try to gradually increase her dose back up to two study pills per day. If she cannot tolerate two study pills per day, she may need to continue at a lower dose for a longer period of time or the duration of the study. If symptoms persist on the lower dosage, encourage her to see her

primary care provider to rule out other causes. Document any study pill dosage changes on *Form 54 - Change of Medications*.

7.3.3 Major Adverse Effects and Events (Required)

Major adverse effects of CaD are expected to be very rare, but may include the development of:

- Renal calculi (kidney stones), or
- Hypercalcemia (increase calcium levels in the blood)

7.3.3.1 Management of Major Health Effects and Events

If a CaD participant reports the following on *Form 17 - CaD Management and Safety Interview* and/or *Form 33 - Medical History Update (Detail)*, permanently discontinue her study pills and record this action on *Form 7 - Participation Status*:

- The development of renal calculi
- The development of hypercalcemia
- Kidney failure requiring dialysis requires a participant to permanently stop taking her CaD study pills. Dialysis raises a safety concern because Vitamin D absorption is likely to be compromised in renal failure participants.
- She is taking calcitriol (e.g., Rocaltrol, Calcijex) (until she discontinues it)
- She is taking > 1,000 IU Vitamin D in personal use (until she is taking < 1,000 IU)

Other major health events may result in the temporary discontinuation of CaD study pills, including:

- Any hospitalization
- Diagnosis of osteoporosis
- Myocardial infarction
- Accidents resulting in immobilization
- Stroke
- **Or** any severe illness in which the administration of calcium/vitamin D is temporarily inappropriate

The decision to temporarily stop CaD study pills is made by a CC PI, physician-designee, or the participant's health care provider. Although taking CaD in the situations above is not likely to be contraindicated, the attending physician may wish to temporarily suspend all medications while a participant is under treatment and administer only medications specific to the condition being treated. Report all decisions to temporarily stop study pills on *Form 54 - Change of Medication*. Complete a second *Form 54* when study pills are resumed. Complete a *Form 7 - Participant Status* if study pills are stopped for more than 3 months.

7.3.4 Unblinding (Required)

The CaD component is a double-blind trial; all CC personnel and CaD participants are blinded to a participant's treatment arm. In addition, all Bone Density site CC staff, other than the person doing the bone densitometry, should be blinded to any loss or gain in bone mineral density.

In some instances of serious adverse effects, the primary care provider may want the participant to be unblinded. If the CC PI or physician-designee decides that unblinding is necessary, the CC Unblinding Officer

will execute the WHILMA database unblinding function, which will require input of data regarding rationale for unblinding. (See *Vol. 5 - Data System, Section 6.5 - Unblinding Procedures*.) WHILMA will provide the treatment assignment and automatically log the unblinding event in the database.

The Unblinding Officer will provide the treatment assignment information only to the CC PI, physician-designee, or primary care provider, as appropriate. Outcomes ascertainment bias can be minimized by maintaining participant blinding, even when unblinding of some personnel becomes necessary. Document in the participant's file that unblinding has occurred, but do not record the treatment assignment in the participant's file.

Figure 7.1
CaD Consent Script

Suggested Script for CaD Consent:

"There are several points I would like to go over with you about the Calcium and Vitamin D trial. I'm sure you have several questions about this part of the study, and this information may answer some of these questions.

As with all parts of the Women's Health Initiative, taking part in the Calcium and Vitamin D trial is completely voluntary and you may drop out at any time. You may choose to answer or not to answer any questions on the study forms. Any information that you give is kept confidential and will only be seen by WHI staff and, if necessary, the Food and Drug Administration (FDA). All of your answers are grouped with the answers of other women in the study, and only this grouped information is released. Neither your name nor any other type of identifying information will be released in any reports.

You can join the Calcium and Vitamin D trial if you don't have health problems that might make taking the pills unsafe for you. Women who join the Calcium and Vitamin D trial will be placed by chance in either a 'Comparison' group or a 'Calcium and Vitamin D' group. A computer makes the selection for the groups so that it is fair. No one knows beforehand who will be in each group or has anything to do with what group you will get. Before you sign up, you must be willing to take part in either group. Both are equally important because everything we learn will come from comparing the groups. Once you begin, no one can take your place in the study group to which you've been assigned.

Women in both groups will be taking study pills. If you're in the Comparison group, you'll be taking pills that don't contain any supplements. If you're in the Calcium and Vitamin D group, you'll be taking pills that contain Calcium and Vitamin D.

You will be placed by computer into one of the groups and neither you nor the Clinic staff will know to which group you have been assigned. However, if there is some kind of medical emergency we can, if necessary, quickly find out which group you're in and give this information to your doctor.

When you join, you'll be asked to take a study pill twice a day with meals. You will be given a choice between two types of study pills, one you can chew and the other you can swallow.

Regardless of which group you're placed in, you may make follow-up visits to the Clinical Center as often as every six months to see how you're doing and to give you more study pills. Calcium and Vitamin D activities during these visits will take about 15-30 minutes.

Your participation in the other WHI clinical trial components will not change regardless of your decision about the Calcium and Vitamin D trial. Participation in the Calcium and Vitamin D trial will not involve any additional tests or procedures.

Occasionally, women who take Calcium and Vitamin D may experience symptoms or side effects. These symptoms may include constipation, heartburn, upset stomach, gas, or bloating. Not all of you will have these symptoms and for those who do, they may be somewhat different for each woman. Most of the time these symptoms are mild and not harmful, but you should contact the Clinical Center if any of the symptoms become severe or too uncomfortable.

Very rarely, serious problems like kidney stones or high calcium in the blood could happen. If so, the Clinical Center staff will stop your study pills so that these problems won't get worse. The health care professionals here are very concerned for your safety and will check regularly for the development of these problems.

Remember, you can call the Clinical Center at any time if you're having any problems or if you have any questions. Do you have questions at this time?"

Figure 7.2

Swallowable CaD Scripts for Participants Randomized to CaD

A. CaD ADHERENCE SCRIPT (for participants who have dropped):

There has been an exciting new change in the Calcium and Vitamin D program! Other women in the Calcium and Vitamin D program, like you, have stopped taking their pills, because they really did not like the taste or texture of the chewable tablet. Now the study pills come in a pill form you can swallow. These new pills can be taken with water, like any other pill. You would still take one of these pills twice a day with meals, and you would still get either the active or inactive (placebo) form, just like when you took the chewable tablets.

We invite you to think about trying this new pill and continue to be a part of the Calcium and Vitamin D program. This is a very important study that will give us many answers to questions about osteoporosis, broken bones, and cancer. We do appreciate your continued efforts in this very important study and for being a part of the answer in WHI.

B. CaD UPDATE SCRIPT (for participants with problems with the chewable formulation):

There has been an exciting new change in the Calcium and Vitamin D program! Now the study pill comes in a pill form you can swallow. These new pills can be taken with water, just like any other pill. You would still take one of these pills twice a day with meals, and you would still get either the active or inactive form, just like when you took the chewable tablets.

If you do not have a problem now taking the tablet that you chew, you probably should continue with that. However, if you are having a problem, you should consider switching to the pill you swallow. If you do choose to switch to the new pill, we want you to know that you can always switch back to the other tablet at your next visit.

The Calcium and Vitamin D study will give us many answers to questions about osteoporosis, broken bones, and cancer. We do appreciate your continued efforts in this very important study and for being a part of the answer in WHI.

C. SWALLOWABLE CaD INTEREST SCRIPT (for participants interested in the new swallowable CaD):

These new study pills were developed because some women did not like the chewable form. Let me show you the new study pill that can be swallowed (*drops a swallowable pill from "test" bottle into the bottle cap*). Would you like to try taking it now?

If yes, drop the pill from the bottle cap into the participant's hand and give her a small cup of water and continue with script. If no, just continue with script:

You would just take one of these pills twice a day with food. Remember, you were assigned to either an active or inactive pill when you joined the CaD program. This new pill comes in both an active and inactive pill form—neither you nor the WHI staff know which form you're taking.

If she chooses to take the new pill form, dispense a six-month supply only. Do not dispense more than a six-month supply until the participant has tolerated at least a full-year's worth of one of the formulations.

Section 7
Calcium and Vitamin D Intervention

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